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One-pot three-component synthesis of α-amino nitriles catalyzed by nano powder TiO_2 P 25

Seyed Meysam Baghbanian[a,*], Maryam Farhang[b], Robabeh Baharfar[b]

[a] *Chemistry Department, Islamic Azad University, Rasht Branch, Pole-taleshan, PO Box 41325-3516, Rasht, Iran*
[b] *Department of Chemistry, Mazandaran University, Babolsar 47415, Iran*

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Abstract

A simple and efficient method has been developed for the synthesis of α-amino nitriles from aldehydes, amines and trimethylsilyl cyanide (Me_3SiCN) in the presence of a catalytic amount of cyanuric acid at room temperature.

Keywords: Nano powder TiO_2 P 25; α-Amino nitriles; One-pot three-component synthesis; Strecker reaction; Trimethylsilyl cyanide

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The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α-aminonitriles. α-Aminonitriles are especially potent representatives of bifunctional compounds. Importance of amino moiety for drug design is hard to overestimate due to a set of intrinsic properties, *i.e.* ability to act as hydrogen bond donor and acceptor or to be involved into electrostatic interactions (after protonation), diversity of chemical modification pathways (acylation, alkylation, reductive alkylation reactions), predictable chemical reactivity and reliability of chemical transformations allowing their use in combinatorial synthesis. Recently, modified method using one-pot procedure *via* a three-component condensation of aldehyde, amine and trimethylsilyl cyanide catalyzed by Lewis acids in conventional organic solvents has been described [1]. However, many of these reported methods involved the use of expensive, moisture sensitive, non-recyclable regents, and required extended reaction times and harsh conditions. Therefore, it is still desirable to improve an efficient and practical method for the Strecker reaction. In order to avoid partially this inconvenience, diethylaluminium cyanide, acetone cyanohydrin, TMSCN, *etc.* have been introduced as cyanide sources in the Strecker reaction [2]. Considering the importance of the Strecker reaction for providing various chiral amino acid precursors in both laboratory and industrial scale, it is highly desirable to develop heterogeneous catalysts. However, there are only few reports that are published on Strecker reaction by using heterogeneous catalysts [3]. Catalytic applications of titanium dioxide have been studied for decades regarding the elimination of environmental pollutants and, more recently, for photocatalytic processes concerning the degradation of pollutants in air, water and soil [4]. Degussa TiO_2 (P 25) is a well known and widely investigated catalyst and photocatalyst. Acid–base and redox properties are one of the most important types of surface chemical properties that in Table 1 properties of TiO_2 P 25 summarized.

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* Corresponding author.
E-mail address: m.baghbanian@iaurasht.ac.ir (S.M. Baghbanian).

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Table 1
Properties of TiO_2 P 25.

Degussa TiO_2 P25 (powder)	Unit	Properties
50 ± 15	m^2/g	Specific surface area (BET)
3.5–4.5		pH in 4% dispersion
21	nm	Average primary particle size
A/R (80/20)[a]		Phase

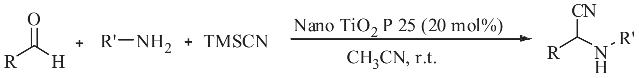
[a] A: anatase; R: rutile. Mass ratios of A/R were listed in the parenthesis.

As part of our current studies on the development of new catalysts [5], herein, we report an efficient and environmentally friendly method for the synthesis of α-aminonitriles catalyzed by Nano TiO_2 P 25 in acetonitrile at room temperature (Scheme 1).

1. Results and discussion

Benzaldehyde, aniline and TMSCN were selected as the model reaction to examine catalytic activity of nano TiO_2 P 25 at ambient temperature. To indicated the need of TiO_2 P 25 for this condensation. We observed that the model reaction did not proceed in the absence of TiO_2even after 12 h (Table 2, entry 1). When using catalytic amount of 10 mol% TiO2 P 25, the reaction gave α-aminonitriles with 70% yield in 10 min in CH_3CN (Table 2, entry 3), and further lowering the catalyst loading up to 5 mol% led to lower yield of 55% in 10 min (Table 2, entry 2). In the presence of 20 mol% catalyst the reaction affords the corresponding 2-phenyl-2-(phenylamino)acetonitrile in 98% yield within 10 min (Table 2, entry 4), and TiO_2 P 25 (25 mol%) also gives 98% yield in 10 min (Table 2, entry 5). The solvents examined were dichloromethane, tetrahydrofuran, and acetonitrile, among whichacetonitrile is shown to be the best (Table 2). Accordingly, 20 mol% TiO_2 P 25 catalyst loading in CH_3CN is considered optimal for the synthesis of α-aminonitriles.

To word, we prepared a range of α-aminonitriles under the optimized conditions (Table 3). Both aromatic and aliphatic aldehydes as well as α,β-unsaturated ones and different amines were coupled with TMSCN under these reaction conditions. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a short reaction time. The reaction of benzaldehyde with aniline and benzyl amine is completed within 10 min with 98 and 93% yield, respectively (Table 3, entries 1 and 2). Therewith, the reaction of benzaldehyde with diethyl-amine is completed within 10 min with 96% yield (Table 3, entries 3). Similar reaction of *p*-methoxy, *m*-phenoxy-benzaldehyde or *p*-tolualdehyde with aniline produces the corresponding products in excellent yield of 93, 89 and 98% in 10, 12 and 14 min, respectively (Table 3, entries 4–6). This method is equally effective with electron-withdrawing 4-chlorobenzaldehyde, 4-fluorobenzaldehyde and 2-cyanoaniline (Table 3, entries 7–10). It should be noted that the reaction of 4-nitrobenzaldehyde and benzyl amine gave no desired product. This illustrates that strongly electron-withdrawing substituent such as p-nitro may not product in



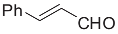
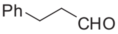
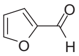
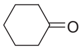
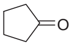
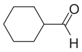
Scheme 1. Strecker reaction in CH_3CN.

Table 2
Three-component synthesis of α-aminonitriles under various conditions[a].

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	No catalyst	12 h	0
2	5	10 min	55
3	10	10 min	70
4	20	10 min	98
5	25	10 min	98
6	20	15 min	86[c]
7	20	25 min	90[d]

[a] TiO_2 P 25 was added to a mixture of 1 mmol of benzaldehyde, 1 mmol of aniline, and 1.2 mmol of TMSCN.
[b] Isolated yield.
[c] In the presence of $CHCl_3$.
[d] In the presence of THF.

Table 3
Preparation of various α-amino nitriles in the presence of nano TiO_2 P 25 in CH_3CN at room temperature[a].

Entry	Aldehyde/ketone	Amine	Time (min)	Yield (%)[b]
1	C_6H_5CHO	$C_6H_5\text{-}NH_2$	10	98 [1f]
2	C_6H_5CHO	$C_6H_4CH_2\text{-}NH_2$	10	93 [6]
3	C_6H_5CHO	$(CH_3CH_2)_2NH$	10	96 [7]
4	4-Me-C_6H_4CHO	$C_6H_5\text{-}NH_2$	14	98 [8]
5	4-MeO-C_6H_4CHO	$C_6H_5\text{-}NH_2$	10	93 [8]
6	3-PhO-C_6H_4CHO	$C_6H_5\text{-}NH_2$	12	89 [1i]
7	4-Cl-C_6H_4CHO	$C_6H_5\text{-}NH_2$	10	97 [1i]
8	4-F-C_6H_4CHO	$C_6H_5\text{-}NH_2$	10	95 [9]
9	4-Cl-C_6H_4CHO	$(CH_3CH_2)_2NH$	14	98 [10]
10	4-Cl-C_6H_4CHO	$C_6H_{11}NH_2$	10	91 [11]
11	4-Nitro-C6H4CHO	$C_6H_5CH_2\text{-}NH_2$	1 h	N. R. [11]
12		$C_6H_5\text{-}NH_2$	8	97 [1f]
13		$C_6H_5\text{-}NH_2$	12	90 [11]
14		$C_6H_5\text{-}NH_2$	12	99 [1f]
15	2-Thienyl-CHO	$C_6H_5\text{-}NH_2$	20	92 [8]
16	i-C_4H_9-CHO	$C_6H5\text{-}NH_2$	25	80 [12]
17	i-C_9H_{17}-CHO	$C_6H_5\text{-}NH_2$	25	78 [1j]
18		$C_6H_5\text{-}NH_2$	1 h	85 [13]
19		$C_6H_5\text{-}NH_2$	1 h	88 [13]
20		$C_6H_5\text{-}NH_2$	1 h	98 [14]

[a] Reaction conditions: aldehyde (1 mmol), aniline (1 mmol), TMSCN (1.2 mmol), TiO_2 P 25 (20 mol%), room temperature, acetonitrile.

[b] The spectral data (^1H, ^{13}C NMR) of known compounds were found to be identical with those reported in the literature [1–13].

Strecker reaction (Table 3, entry 11). Furthermore, the reaction conditions are mild enough to perform these reactions with acid sensitive aldehydes such as cinnamaldehyde, 2-furaldehyde and 2-thiophene-2-carbaldehyde which form the corresponding aminocyano compounds in good yield (Table 3, entry 12, 14 and 15). This may indicate that the catalytic system selectively activates the carbonyl function and keeps the furan or 2-thienyl ring and double bond of cinnamaldehyde intact. While, the reaction of hydrocinnamaldehydepentanal and decanal gives the corresponding products in 90%, 80% and 78% yield, respectively (Table 3, entries 16 and 17). The reaction of cyclohexanone and cyclopentanone with aniline produces the corresponding products in 85 and 88% yield in 'longer' reaction time (1 h), respectively (Table 3, entries 18 and 19). Moreover, the reaction cyclohexanecarbaldehyde with aniline give the corresponding product in 98% yield in 1 h (Table 3, entry 20). This indicates that aliphatic aldehydes lower yield with 'longer' reaction time (1 h). Moreover, we continued our exploration of the synthesis α-aminonitriles by treating various amines with aldehydes and TMSCN under similar reaction conditions. Different aromatic and aliphatic amines were used in the reaction and they underwent efficient coupling with benzaldehyde and TMSCN as shown in Table 3. The recycling of catalyst was achieved through filtration followed by washing with acetonitrile and the recycled catalyst obtained thus was sufficient for its reuse. For example, the reaction of benzaldehyde, aniline, and trimethylsilyl cyanide gave the corresponding α-aminonitriles (Table 3, entry 1) in 98%, 97%, and 95% yields over three cycles.

To conclude, we have shown that the nano TiO_2 P 25 is a highly active, reusable catalyst for the synthesis of α-amino nitriles. General procedure for the preparation of α-aminonitriles: A mixture of amine (1 mmol), aldehyde (1 mmol), trimethylsilylcyanide (1.2 mmol) and nano TiO_2 P 25 (20 mol%) in CH_3CN (1 mL) was stirred at ambient temperature for an appropriate time (Table 2). After completion of the reaction as indicated by TLC, the nano TiO_2 P 25 was filtered and washed with acetonitrile (2× 10 mL). The crude product was purified by recrystallization from diethyl ether (solid products) or by chromatography using silica gel and mixtures of hexane/ethyl acetate of increasing polarity. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature [1f,j, 6–14]. The isolated yields were in good agreement with those obtained by GC analysis [1–13]. Spectroscopic data for a selected example; (Table 2, entry 1) [1f]: Solid, mp 75–76 °C, IR (KBr): ν 3349, 3016, 2965, 2276, 1643, 1565. ^1H NMR ($CDCl_3$): δ 4.15 (d, 1H, $J = 8.1$ Hz), 5.43 (d, 1H, $J = 8.1$ Hz), 6.65 (d, 2H, $J = 8.0$ Hz), 6.86 (t, 1H, $J = 7.8$ Hz), 7.45 (t, 2H, $J = 7.8$ Hz), 7.45–7.58 (m, 3H), 7.50–7.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 50.5, 112.5, 119.9, 123.7, 126.9, 129.9, 130.0, 130.2, 135.5, 147.5. EIMS: *m/z*: 208 M^+, 180, 116, 91, 77, 51. Anal. Calcd. for $C_{14}H_{12}N_2$ (208.26): C, 80.74; H, 5.81; N, 13.45. Found: C, 80.53; H, 5.74; N, 13.89%.

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